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Is Intranasal Oxytocin an Effective Treatment for Reducing Disruptive Behavior in Individuals with Prader-Willi Syndrome?

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not intranasal oxytocin is an effective treatment for reducing disruptive behavior in individuals with Prader-Willi Syndrome.

STUDY DESIGN: This is a systematic review of two randomized controlled crossover trials and one randomized controlled pilot study, all of which were double-blind and placebo-controlled. All articles were peer-reviewed, written in English and published between 2011 and 2016.

DATA SOURCES: The three articles used in this systematic review were found in PubMed based on their relevance to the objective of the study, the inclusion of patient-oriented problems and published within the last 10 years.

OUTCOMES MEASURED: The outcomes measured for this review are the individual's disruptive behavior and whether there was an improvement after administering intranasal oxytocin. One study used a questionnaire rated by parents of children with Prader-Willi Syndrome, another used a developmental behavior checklist version M to rate temper outburst and the last study scored disruptive behavior on a grid by a team of psychologists.

RESULTS: Two of the three studies demonstrated no statistically significant improvement in disruptive behavior in individuals with Prader-Willi syndrome.^{6,8} Kuppens *et al.* with no statistical significance demonstrated as group 6-11 years old had a p-value of 0.071 and age 11-14 with p-value of 0.109.⁶ Einfeld *et al.* demonstrated an increase in temper outbursts when a higher dose of oxytocin was administered with p-value of 0.01.⁷ Tauber *et al* resulted in statistically significant reduction in disruptive behavior in the late effect with p-value 0.031 but overall, the data documented no significance in the reduction of disruptive behavior.⁸

CONCLUSIONS: The use of intranasal oxytocin to reduce disruptive behavior is promising, however, the current data on the use of intranasal oxytocin to reduce disruptive behavior in individuals with PWS is inconclusive. Each study demonstrated a different conclusion on the data ranging from increasing disruptive behavior to decreasing disruptive behavior. Consequently, more research is needed in order to draw a formal conclusion on the use of intranasal oxytocin and its potential effects on behavior in individuals with Prader-Willi syndrome.

KEYWORDS: Prader-Willi Syndrome (PWS) and Oxytocin

INTRODUCTION:

Prader-Willi Syndrome (PWS) is a genetic disorder involving chromosome 15 and the hypothalamus. PWS affects appetite, growth, metabolism, cognitive function and behavior with typical features including: short stature, decreased muscle tone, incomplete sexual development, intellectual disability, and insatiable hunger leading to obesity.¹ In PWS, the hypothalamus is unable to regulate hunger and satiety but the direct cause as to why this occurs is unknown. The etiology of PWS is either a genetic deletion or mutation of chromosome 15 occurring spontaneously at or near conception for unknown reasons.² PWS affects males and females equally and occurs in all ethnic groups and geographic regions worldwide without a significant commonality among a certain population.¹ PWS is estimated to affect 12,000-15,000 individuals in the United States and about 350,000 individuals worldwide, making PWS the most common genetic cause of obesity.^{3,4}

PWS is usually diagnosed with a blood test and may be picked up on a well-child exam. Very few specialists for PWS exist, meaning their care starts with their Primary Care Provider (PCP). PWS takes a team of healthcare professionals, including physician assistants in different specialties ranging from mental health to endocrinology. The number of healthcare visits per year is unknown but is substantially greater than a patient without PWS. Healthcare visits range from 18-150 visits per year and correlate with age, with the most frequent visits per year being age 41-64 years.² The exact annual healthcare cost for an individual with PWS is unknown, however, one study reported that the average annual cost per person ranges from \$82,321-\$134,395.⁵ The large number of healthcare visits and expense could be attributed to the lack of specialists for PWS and an inability to effectively care for these individuals due to a lack of expertise on the condition.

PWS is treated in a similar fashion as Autism, in that, the person is treated individually based on the needs of their symptoms. Common treatments include Human growth hormone (hGH) supplement for short stature, sex hormone therapy to promote sexual maturation, weight management, CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure) machine for sleep disorders such as sleep apnea and a psychiatrist or psychologist for mental health care.³

The method of using intranasal oxytocin is being proposed to treat PWS because the oxytocin system in PWS patients is dysfunctional and there is currently no standard treatment for behavioral problems and hyperphagia in these individuals. Oxytocin is known to affect body weight, feeding schedules, and social skills.⁶ Intranasal oxytocin is thought to positively impact and regulate behavior and hyperphagia in PWS and this paper evaluates three different randomized controlled trials (RCTs) comparing the efficacy of intranasal oxytocin as a treatment to reduce disruptive behavior in those with PWS.

OBJECTIVE:

The objective of this selective evidence-based medicine (EBM) review is to determine whether or not intranasal oxytocin is an effective treatment for reducing disruptive behavior in individuals with Prader-Willi Syndrome.

METHODS:

The studies used in this systematic review were researched by the author in both Cochrane Library and PubMed. All the studies for this systematic review were located via PubMed using keywords “Prader-willi syndrome” and “oxytocin”. To be selected, the article must be a randomized, controlled, double-blind study involving individuals with PWS, be peer-reviewed and published within the last 10 years. In addition, each study must have evaluated

patient-oriented outcomes (POEMS) that pertained to the clinical question regarding disruptive behavior reduction. Articles were excluded if they did not pertain to the clinical question or if their publication date was greater than 10 years old.

Each article used in this study was published in English in a peer-reviewed journal, one in Orphanet Journal of Rare Diseases, one in American Journal of Medical Genetics, and one in Clinical Endocrinology.⁶⁻⁸ Of the articles selected, there were two randomized, controlled crossover trials and one randomized, controlled pilot study, all of which were double-blind, and placebo-controlled. Each study included a population of individuals with PWS with an intervention of intranasal oxytocin in comparison to intranasal placebo groups, with at least one - outcome measurement involving POEMS of disruptive behavior/temper outbursts.⁶⁻⁸ Statistics used in these studies include: P-value, Wilcoxon and Mann Whitney test. Table I, seen below, summarizes the demographics and characteristics observed in each study.

Table 1: demographics & characteristics of included studies

Study	Type	#pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W /D	Intervention
Kuppens ⁶ (2016)	Randomized controlled crossover trial (double-blind, placebo-controlled)	25	6-14	Genetically confirmed dx of PWS Age 6-14 Social behavioral problems and/or preoccupation with food Were naïve of oxytocin treatment at time of enrollment Used hGH for at least 1 year and still receiving it	Severe psychiatric problems Allergic reactions/hypersensitivity to oxytocin Medication to reduce weight/fat other than GH Noncooperative behavior resulting in inability to comply with intranasal administration	0	Syntocinon Intranasal oxytocin dose range 12 IU -24 IU BID dependent on body surface area for 4 weeks

					and or hospital visits		
Einfeld ⁷ (2014)	Randomized controlled crossover trial (double-blind, placebo-controlled)	30	12-29	PWS diagnosis and genetic subtype established No known hypersensitivity to preservatives in the nasal spray viz E216, E218 and chlorobutanol hemihydrate	Mental age below 8 years old	8	Intranasal Oxytocin 11 patients 18+ → 24 IU BIDx8weeks 13-15y/o → 18 IU BIDx8weeks 18 patients 18+ → 40 IU BIDx8weeks 13-15y/o → 32 IU BIDx8 weeks
Tauber ⁸ (2011)	Randomized Controlled Pilot Study (double-blind, placebo-controlled)	24	18-43	Genetically confirmed diagnosis of PWS	Abnormal ECG Other severe cardiac problems	0	Syntocinon Intranasal oxytocin, single dose 24 IU Saline placebo

OUTCOMES MEASURED:

In Kuppens *et al.*, the outcomes measured were hyperphagia and social behavior including happiness, anger, sadness, conflicts, social interaction, and disruptive behavior.⁶ The outcome that was measured in which this study will focus on is disruptive behavior. In order to measure the outcome, the study used an Oxytocin Study Questionnaire completed by parents rating child's behavior from -3 (much less frequent) → +3 (much more frequent) where a decrease in 4 points is considered clinically relevant.⁶ Based on that questionnaire, disruptive behavior was then categorized as better, the same or worse from baseline throughout the course of the study in both the patients receiving oxytocin and the patients receiving a visually matched

placebo.⁶ These ratings were then used to determine the statistical significance of the outcomes measured using the Wilcoxon test and p-values.

In Einfeld *et al.*, the primary outcomes measured were hyperphagia/pica and temper outbursts.⁷ Again, the outcome that is the main focus of this systematic review is temper outbursts which are descriptive of disruptive behavior. A Developmental Behavior Checklist version M (for monitoring) rating behavior from 0-3 on multiple items, including temper outburst was utilized.⁷ This rating was performed by the participant's caregiver/parent (0= not a problem today and 3= major problem today).⁷ To analyze the statistical significance of the outcomes measured, the difference between the rates of change score for items in the two treatment conditions, along with p-values were used.

In Tauber *et al.*, the primary outcomes addressed were behavior items including isolation tendencies, sadness tendencies, depressive tendencies, self-depreciation, self-mutilation, conflicts with others, disruptive behavior (including temper outbursts), interests in friendships, interest in love affairs, and trust in others.⁸ This systematic review has a main focus on the disruptive behavior/temper outbursts which were measured as an outcome in this study. Tauber *et al.* used a team of psychologists that carefully monitored and scored behaviors on a behavior grid daily.⁸ The grid used to measure the outcomes was created by the caregivers, based on routine observation of these patients.⁸ From the scoring, p-values, Mann-Whitney test and Wilcoxon test were used to evaluate the statistical significance of the outcomes measured.

RESULTS:

The three studies in this systematic review all addressed the effectiveness of oxytocin to reduce disruptive behavior in some capacity. One RCT pilot study and two randomized crossover

trials were used. All data presented on this topic was provided as continuous data with p-values that were unable to be converted into dichotomous data.

Kuppens *et al.* was a randomized controlled crossover study involving participants ranged from age 6-14 years old with a median age of 9.3 years, all children were also receiving growth hormone during the study.⁶ Participants were examined at an outpatient clinic at baseline, after 4 weeks and after 8 weeks with behavior being documented at home. This study did not involve a washout time period. The study group consisted of 25 children (n=25), 14 boys and 11 girls all with PWS, all of whom were compliant, completed the study and were included in the results of the study.⁶ The results used in calculating the data were split between two sets of groups. Of the original analysis of the entire group, no significant effects of oxytocin on behavior were found, however, the results demonstrated beneficial effects on total social behavior in younger participants and a sub-analysis was performed on participants age 6-11 (n=17) and those 11-14 (n=8).⁶ For this study disruptive behavior is specifically analyzed and based on the Wilcoxon Test, no statistical significance was demonstrated as group 6-11 years old had a p-value of 0.071 and age 11-14 with a p-value of 0.109 ,where p-value ≤ 0.05 is statistically significant (see table 2 below). The intranasal oxytocin was not found to have any side effects or safety concerns during this study.⁶

Table 2: Effects on disruptive behavior of children younger and older than 11 years⁶

Disruptive Behavior	Oxytocin Phase			Placebo Phase			P-value
	Better	Same	Worse	Better	Same	Worse	
Age 6-11 N=17	4	13	0	1	13	3	0.071
Age 11-14 N=8	0	5	3	2	6	0	0.109

Einfeld *et al.* was a randomized controlled crossover study involving 30 recruited participants age 12-29 with PWS.⁷ Of the 30 participants 25 participated in phase 1 and 22 participants completed the crossover (phase 2); leaving 22 participants eligible for analysis (n=22).⁷ The 22 participants were divided into 2 groups, one receiving a low dose of oxytocin and the other a high dose oxytocin. Participants temper outburst results were then compared from placebo to oxytocin and oxytocin low dose versus high dose. The results included a mean change from placebo to oxytocin phases with standard deviation (SD) along with p-values to determine statistical significance. The change in temper outburst mean from placebo mean 1.31 (1.23 SD) to oxytocin mean 2.16 (1.92 SD) is 0.85 increase in mean showing increase in temper outburst with oxytocin administration giving $p = 0.023$.⁷ The increase in temper outburst for higher dose oxytocin was significant with $p = 0.01$ overall, but for low dose oxytocin the change was not statistically significant with $p = 0.746$.⁷ No side effects or safety concerns were reported during this study.⁷

Table 3: Mean and Standard Deviations for DBM-M temper outbursts⁷

	Placebo	Oxytocin	Oxytocin Low dose	Oxytocin High dose
Temper Outburst	1.31 (1.23)	2.16 (1.92)	1.12 (1.05)	2.62 (2.06)
Change from placebo/baseline	n/a	0.85 increase	0.19 decrease	1.31 increase
p-value	n/a	0.023	0.746	0.01

Tauber *et al.* was a randomized controlled pilot study involving 24 adults with PWS age 18-43 years old.⁸ Of the 24 participants, 16 were female and 8 were male with a median age of 28.5 years.⁸ The study was conducted in a dedicated PWS center where patients are regularly admitted for one month and live in a controlled environment.⁸ Patients were put into pairs of the same gender and same IQ range and given a single dose of either oxytocin (OT) or placebo in a double-blind randomization. The study took place over the course of three series of admissions.⁸

Results were reported in mean change from pre-administration, early effect (the half day following administration) and late effect (2 days following administration) along with a mean change in behavioral scores analyzed with Mann Whitney and Wilcoxon tests. Results for disruptive behavior in the late effect group were statistically significant with $p = 0.031$ and the pre-post difference was statistically significant for the oxytocin group with $p = 0.011$.⁸ Pre-administration placebo group had mean scores -0.0361 ± 0.354 , OT -0.431 ± 0.344 with p-value 0.744 (Table 4).⁸ Early effect mean scores were placebo with -0.250 ± 0.452 and OT with -0.167 ± 0.389 with p-value 0.623; late effect mean scores were placebo with -0.306 ± 0.382 and OT with -0.042 ± 0.144 with p-value 0.031 (Table 4).⁸ The change in mean from pre-post disruptive behavior scores are as follows; placebo mean 0.056 (0.457 SD) with $p = 0.812$, OT group mean 0.389 (0.385SD) with $p = 0.011$ and OT versus placebo Wilcoxon p-value of 0.070 (Table 5).⁸ No side effects or safety concerns were reported during this study.

Table 4: Mean disruptive behavior scores pre-and post-administration⁸

Disruptive Behavior	Placebo Group	Oxytocin Group	P-value
Pre-administration	-0.361 ± 0.354	-0.431 ± 0.344	0.744
Early effect	-0.250 ± 0.452	-0.167 ± 0.389	0.623
Late effect	-0.306 ± 0.382	-0.042 ± 0.144	0.031

Table 5: Pre-post behavioral score mean differences⁸

	Placebo Group	Oxytocin Group	Oxytocin vs. Placebo
Mean (SD)	0.056 (0.457)	0.389 (0.385)	n/a
P-value (Mann-Whitney)	0.812	0.011	n/a
P-value (Wilcoxon)	n/a	n/a	0.070

DISCUSSIONS:

This review examines two randomized, controlled crossover trials and one randomized, controlled pilot study, all of which are double-blind, and placebo-controlled. Kuppens *et al.*

evaluated only adults, Tauber *et al.* evaluated only children and Einfeld *et al.* evaluated both adults and children. This reveals an interesting dynamic; although individuals with PWS are known to have disruptive behavior, it is possible that after time, some actions have become irreversible habit versus redirectable behavior leading to the hypothesis that oxytocin may be more beneficial with earlier intervention. In the studies being reviewed, the patients, clinicians and study workers were kept blind and all who entered the trial were accounted for. Of the studies, Kuppens *et al.* had a patient who was on levothyroxine, one patient on citalopram and one patient on aripiprazole, all of which may impact the effects of oxytocin on disruptive behavior.⁶ In Einfeld *et al.* 5 patients were diagnosed with anxiety, 3 with depression and 1 with schizophrenia which may skew the results of the effectiveness of oxytocin at reducing disruptive behavior; however, the results in this study were measured from the individual's own baseline, lessening the likelihood that the results could be skewed.⁷ Tauber *et al.* had a similar issue in that 4 patients in the OT group and 3 in the placebo group were receiving psychotropic medications while involved in the study, again potentially affecting the results.⁸ Although these are weaknesses of the studies, there is currently no effective, consistent treatment plan in place for individuals with PWS to decrease disruptive behavior and the population of study candidates is too small for an adequate sample size.

Tauber *et al.* is the only study in which follow-up does not appear to be long enough. The participants were followed two days prior to, and 2 days after, administration of oxytocin; there may have been change in behavior outside of the follow up period.⁸ However, these individuals were regularly seen and evaluated by staff and it is much more likely that the psychologist team would have picked up on even subtle differences over the 4 day total time period.

Einfeld *et al.* was the only study to have withdrawals and loss to follow up. Of the initial number beginning the study, 5 individuals never received the initial phase for personal reasons or relocation and 3 were lost to follow up after phase 1.⁷ This did exclude the participants from final data analysis, however, the final sample size remained adequate at 22 participants.

There appears to be no standardized and commonly accepted rating scale for evaluating disruptive behavior, let alone the effects of oxytocin in decreasing it. The evaluation in all studies was subjective. In some instances, the disruptive behavior increased but, were the increases in frequency, duration, intensity or some combination thereof? This is compounded by the size of the studies. PWS is not a common condition, so having an adequate sample size in one location presents barriers.

Currently, the intranasal form of oxytocin is not FDA approved; however, it is available in Europe.⁹ Due to the lack of FDA approval, intranasal oxytocin is not able to be covered by insurance in the United States. There are several sellers of the product for research purposes, but regulations do not exist, making an unreliable medication. Oxytocin is available in the United States in intramuscular (IM) and intravenous (IV) formulations, but these were not the forms administered in this study. The IM and IV forms carry with them cardiovascular effects, antidiuretic effects, and potential maternal death.¹⁰ Due to these potential negative effects, Tauber *et al.* excluded individuals from their study if they had an abnormal electrocardiogram.⁸

Limitations in searching for articles included the small number of studies on PWS in general, the number of studies conducted using oxytocin, and finding studies that specifically used intranasal oxytocin. There are few studies on PWS and even fewer on intranasal oxytocin with individuals who have PWS. This led to a selection of studies with a wide range of ages and dosages of oxytocin.

Limitations of the studies used included the wide range of dosing, lack of plasma levels of oxytocin obtained. In addition, the studies include individuals with PWS without regard to whether the PWS was a chromosomal deletion or mutation. Although the participants were specified to have deletions or mutations, there was an inability to separate out the groups and maintain an adequate sample size for data evaluation.

CONCLUSION:

Research on the use of intranasal oxytocin to reduce disruptive behavior is promising, however, the current data on the use of intranasal oxytocin to reduce disruptive behavior in individuals with PWS in this systematic review is inconclusive. All three of the studies in this review provide conflicting data on whether or not intranasal oxytocin decreased disruptive behavior. Einfeld *et al* even found an increase in disruptive behavior in part of the data analysis.⁷ Further studies are needed to discover a more concrete and significant answer to the question this review set out to ascertain. Due to some of the flaws of these studies, future studies need a more congruent population age, a longer duration of treatment and would benefit from the separation of individuals with gene deletion versus mutation. Based on the results of these studies, it would be warranted to try and study the effects of oxytocin on younger individuals with PWS and measure the outcomes of disruptive behavior over a prolonged period of time to analyze if the earlier initiation of oxytocin may decrease the development of some disruptive behaviors altogether, as well as provide intervention before the number of oxytocin receptors begin to decrease. As a result of the few medical interventions available for PWS patients, a new intervention to aid in the management of disruptive behaviors and potentially hyperphagia could greatly impact these individuals lives. The only way to discover such an intervention is to continue to research potential solutions.

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